

A National Treatment and Research Agenda for Long Covid

Prepared by LCAP CURE & Steering Committees



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LCAP (Long Covid Action Project)

LCAP is a united group of non-partisan individuals taking action to end the Long Covid crisis through awareness and government accountability. We seek urgent treatment and support for people with Long Covid. We spend twenty-four hours a day researching, living, and communicating about Long Covid. We see this book as a crucial step towards improving research and treatment for this disease.

How-To Guide

This book is designed to serve as a practical resource for researchers, industry, healthcare providers, government, and individuals living with Long Covid. It compiles evidence-based principles for treatment options, models for clinical trials, research recommendations and unmet criteria, each supported by accessible research links to facilitate informed decision-making in clinical settings (see the QR code option to hyperlinks on back of book). For healthcare professionals, this book offers a structured overview of emerging therapeutic approaches, helping them to navigate the evolving landscape of Long Covid care. For the government, this book can be used as a reference to develop new laws and education addressing the disease. For patients, this book serves as an educational tool, equipping them with the knowledge needed to discuss treatment options with their providers, advocate for their needs, and inform others about Long Covid. By bridging the gap between research and real-world application, we hope this book empowers both doctors and patients in their pursuit of effective management strategies.

Introduction

Long Covid occurs when SARS-CoV-2 remains in the body, a condition also known as viral persistence or chronic viral infection. It is a debilitating disease that can damage

organs, neurological, gastrointestinal, and vascular systems as a result of SARS-CoV-2 viral persistence. [1]

More than 5,000 Americans have died from Long Covid, while COVID-19 has killed over 1.1 million people in the U.S.. according to the Centers for Disease Control and Prevention (CDC). [2] However, studies factoring in excess mortality and death certificate changes indicate that both Long Covid and COVID-19 related deaths are underreported. [2][3] For instance, from January 1, 2020 to December 31, 2021, over 18 million COVID-19 deaths occurred worldwide when excess mortality is taken into account, yet only 5.94 million of those deaths were officially attributed to COVID-19. [4]

Research increasingly shows that SARS-CoV-2 persistence can cause AIDS-like immune changes, while Long Covid continues to spread unchecked, affecting over 400 million people worldwide. [5] [6] Despite \$1.812 billion allocated to NIH for Long Covid research, there are still no proven treatments, no cures, and no national treatment or research agenda. [7] [8] As of 2024, an estimated 17% of U.S. adults (45 million Americans) have had Long Covid, in addition to more than 5.8 million children affected by the disease. [9]

NIH also reported a 10% chance of developing Long Covid after a first infection. [10] This number grows daily as COVID-19 continues to spread freely due to the government's failure to educate citizens regarding mitigation measures, especially among healthcare workers, leading to failures in preventing nosocomial infections. [11] Five years have passed, yet the NIH has still failed to develop pre-exposure or post-exposure prophylaxis, or treatment-as-prevention pharmaceutical strategies.

Meanwhile, even among the fittest-of-the-fit, Long Covid is taking a heavy toll. A staggering 25% of young, healthy U.S. Marines experienced long-term effects after Covid infection – posing a clear national security threat to U.S. military readiness, in addition to an estimated \$3.7 trillion dollar drag on the U.S. economy. [12] [13]

14 Principles for a New Long Covid Drug Testing System

To eliminate the serious threats created by Long Covid to U.S. health, national security, and economic stability, the fourteen bold actions listed below are required to improve Long Covid research and treatment. It is important that *all* clinical manifestations presented by viral persistence be considered in applying each of these principles. LCAP calls upon everyone working in the struggle against Long Covid to put these principles to work, prioritizing the establishment of accurate Long Covid biomarkers for viral persistence and immune changes.

1. Antivirals— Research shows that SARS-CoV-2, the virus that causes Covid, persists in the body, and that antiviral treatments, especially if administered early, help neutralize the virus and treat Long Covid. [14] For example, China already successfully uses antivirals such as Azvudine and VV116, and has many more in development.[15][16] [17]

Further supporting their effectiveness, a 2025 Long Covid study found SARS-CoV-2 antivirals helped reduce Long Covid elevated neurodamage markers, while anticoagulants had the opposite effect.[18] The study concluded, “second-line antiviral treatment is the single best predictor of clinical recovery in a real-world Long Covid cohort, supporting a putative role for viral persistence in Long Covid.”[18] Additional antivirals must be explored by researchers as a first line of defense in both preventing and treating Long Covid. (See **Appendix A: Antivirals**)

2. Monoclonal Antibodies— In some states such as Florida, monoclonal antibodies including Regeneron (Casirivimab & Imdevimab) and others were made available under Emergency Use Authorizations. These monoclonal antibodies provided effective treatment in the acute phase of Covid-19. [19] [20] Studies also show favorable results when using monoclonal antibodies to treat Long Covid. [8] [21] Ideally, researchers should conduct trials of monoclonal antibodies in combination therapies rather than relying on single monoclonal antibodies for treating Long Covid.

Unfortunately, the federal government has failed to adequately distribute monoclonal antibodies to the public, missing an excellent opportunity for research and treatment of Long Covid. [22] [23] Drug manufacturers also have been uncooperative at times in failing to supply researchers with drugs for clinical trials. [24] (See **Appendix B: Monoclonal and Polyclonal Antibodies**)

3. Other Drugs of Interest— Appendix C contains a list of many drugs that have been *already approved by the FDA* for other uses. Many of these are not identified traditionally or commonly as antivirals and are not used for Long Covid; nonetheless, they possess antiviral effects or other benefits that could prove invaluable in treating Long Covid. In line with this, some drugs listed in the Appendices are already used for other conditions but show potential in treating Long Covid. These medications could be quickly and safely tested for off-label use. Others on the list are still in early stages of development and warrant further research. As a reminder, many Long Covid patients have been sick for five years and counting and are in dire need of help. (See **Appendix C: Other Drugs of Interest**)

4. Combination therapies— People with Long Covid are frequently reinfected. As a result, they can harbor more than one variant of the Covid virus. This can result in

mutations from viral persistence and recombination of different viral strains in the body. [25] Clinical trials are therefore needed to test combinations of more than one treatment – such as more than one monoclonal antibody (mAbs) including polyclonal antibodies (pAbs), that have proven effective against different SARS-CoV-2 virus strains. Combined treatment regimens, using antivirals *together* with monoclonal antibodies or other drugs, for example, should be trialled to test for more effective treatments.

Research indicates pAbs could prove to be more effective than mAbs, especially in the case of immunocompromised patients, because they offer a wider range of neutralizing antibodies and potentially less risk for SARS-CoV-2 viral resistance.[26] It's important to point out that pAbs should not be removed as Long Covid treatment options because of market factors — such as the limited ability to establish patent rights by drug manufacturers. Patients should not be made to suffer longer simply because of administrative issues. If pAbs can be more effective at reducing or eliminating viral load, then this must become a priority for research within RECOVER (NIH).

5. Biomarkers— A Case for Multi-Omics Sparked By Whole Blood Transcriptomic Analysis — Among ways to test for Long Covid are computer analysis of genes, the genome, RNA, and proteins, each of which could establish a different biomarker; the issue is then which test or tests produce the most reliable biomarker.

As LCAP has argued for parallels to HIV/AIDS viral persistence testing and treatment, researchers in 2025 have answered that call.[27] In a viewpoint paper about targeting Long Covid viral reservoirs, it was stated, “the field would benefit tremendously from a persistence biomarker akin to the plasma HIV RNA level in HIV—an objective measurement that uses an easily accessible body fluid (e.g. blood), is sensitive and specific, has a rapid turnaround time, is scalable, and for which a change (eg, reduction) is clearly associated with a clinical outcome.”[8]

In 2024, a groundbreaking study published in *The Lancet Microbe* by Belgian researchers **using a transcriptomic whole blood analysis** identified **antisense SARS-CoV-2 RNA** and **FYN RNA concentrations** as independent predictors of Long Covid, with **94% sensitivity**. [28] The transcriptomic panel emerged as a particularly powerful tool that offers a convincing case for establishing validated Long Covid biomarkers. A transcriptomic test, something capable of measuring RNA viral load levels, would be the most sensitive, readily available and scalable test for an RNA virus. The discovery of antisense RNA, in particular, suggests the presence of replicating viral material from infected cells, while FYN, a gene involved in immune cell signaling, highlights ongoing immune activation. Using both test results together as biomarkers would provide stronger efficacy in Long Covid trials once validated.

The Belgian study's findings demonstrate the potential of transcriptomic profiling to not only diagnose Long Covid and measure RNA viral load, but also to uncover its underlying biological mechanisms. At the time of this book's publishing, the Belgium research team is working to validate these biomarkers using one hundred internationally sourced whole blood samples of Long Covid patients and comparable control patients. [29]

It is a travesty that no accurate biomarker test for Long Covid has been validated for use after 5 years. Numerous studies have identified biomarker candidates across immune, inflammatory, metabolic, vascular, and neurological pathways, offering insight into the underlying mechanisms of Long Covid. These biomarkers include elevated cytokines (e.g., IL-6, IL-1 β), autoantibodies, endothelial dysfunction markers, microclots, and mitochondrial dysfunction indicators. [30] [31] [32] [33] Due to the heterogeneity of disease outcomes, or differing SARS-CoV-2 variants causing Long Covid, it is difficult for researchers to isolate one specific test.

Many biomarkers, such as dysregulated kynurenine pathway metabolites or oxidative stress markers, lack clear prevalence data, underscoring the challenges of relying on isolated biomarkers for diagnosis or stratification. For proposed biomarker tests like the MENSA test, which relies on measuring antibodies, some Long Covid patients do not produce antibodies and would therefore not test positive, leading to missed cases or misdiagnosis. Additionally, the test can only detect antibodies within a short window of time after infection (the test may fail to detect whether a patient was infected beyond 3 months after infection, leaving out a large swath of patients who have been sick with Long Covid for years.) A blood draw may also fail to pick up infection within immune privileged sites, such as tissues, organs, the brain or bone marrow.

While individual biomarkers are valuable insights into Long Covid, their true potential lies in their integration within a multi-omics framework that's built on a foundation of whole blood transcriptomic analysis. By combining these markers with other omics data, such as proteomic profiles of viral proteins (e.g. spike protein) and inflammatory cytokines, or metabolomic signatures of mitochondrial dysfunction, clinicians could develop a more precise and personalized approach to treating Long Covid.

A multi-omics strategy would also help identify subtypes of Long Covid, enabling targeted therapies for specific patient groups. For example, patients with high antisense RNA levels might benefit from antiviral therapies, while those with elevated FYN expression could be candidates for immune-modulating treatments.

The transcriptomic biomarkers are significant and concerning because they point to viral persistence and immune dysregulation mechanisms that have parallels in chronic viral infections like HIV/AIDS. The use of transcriptomic biomarkers like antisense RNA

and FYN into a wider omics test could revolutionize the diagnosis and management of Long Covid in ways viral load tests changed the trajectory of HIV.

6. Longer study durations— Short duration studies for antivirals allocate insufficient time for understanding the actual effectiveness of antiviral treatments. For example, a study of the antiviral drug Molnupiravir found that a 5-day course of treatment was not long enough to clear the Covid-19 virus. [34] Antiviral studies may require longer-term treatments lasting from several months up to a year for effects to be accurately assessed. Studies lasting merely days or weeks do not allow potential benefits to be realized. [23]

This issue extends beyond antiviral effectiveness. Short duration studies have repeatedly caused public and physician misperceptions of the true duration of Long Covid. Many people who first became sick with Long Covid in 2020 continue to suffer five years later, with no end in sight. The ongoing reality of Long Covid is obscured by the many short-duration research studies—such as two years—that do not reflect the actual ongoing persistence of the condition. Longer duration studies are needed to provide a more accurate and comprehensive understanding of Long Covid.

7. Study the Long-term “Long Haulers” — Failure to study the Long Covid “long haulers” who have been sick for 5 years (and counting) as of 2025 has led researchers to conduct flawed symptom studies. These studies obscure the escalating and worsening symptoms of long-term long haulers by commingling them with those who have been sick for a shorter time. Patients who have more recently acquired Long Covid may initially demonstrate milder symptoms. Current studies often misrepresent the early, less severe cases as the defining symptoms of Long Covid, overlooking more serious symptoms that occur as the disease progresses, and missing the full complexity and long-term impact of Long Covid. [35]

Consequently, the more serious Long Covid long hauler symptoms have been obscured and buried from view. Yet the fallout of Long Covid in cases lasting five or more years includes serious consequences: heart and blood vessel damage, brain damage, neurological damage, vision and hearing damage, organ damage, respiratory problems, strokes, blood clots, Raynaud’s syndrome, Bell’s Palsy, new onset cancers, and other serious new onset conditions including diabetes, accelerated osteoporosis, Parkinson’s, Alzheimer’s, and dementia. Long haulers from 2020 with more serious symptoms have been systematically left out of research and the potential benefits of participating in clinical trials. Yet these earliest long haulers are the canaries in the coal mine, warning of us of what is to come. They must instead be studied, heeded, and treated.

8. Study the Vaccine Injured— Many people developed Long Covid in 2020, before vaccines became available in 2021. Once vaccines became widely available, reports emerged of vaccine-related injuries leading to Long Covid. [36] Some 2020 Long Covid patients also reported experiencing worsening symptoms from subsequent Covid-19 vaccinations, while other Long Covid patients reported benefits or even improvements from vaccination. [37] [38] [39] To further complicate matters, some Long Covid patients received the vaccine but failed to generate antibodies. Still other patients were so ill with Long Covid that doctors advised against Covid-19 vaccines for fear of worsening their condition.

This raises broader concerns about vaccine effectiveness and design, as none of the vaccines available are “one and done” sterilizing vaccines. In fact, not all Covid-19 vaccines are even of the same type, ranging from mRNA-based vaccines developed by Pfizer and Moderna, to AstraZeneca’s viral vector vaccine, to a protein-based vaccine created by Novavax. Studying vaccine-injured people with Long Covid would provide valuable data to improve future vaccines, treatments, and cures while expanding our understanding of the interaction between Covid-19 vaccines and Long Covid.

9. Research Subject Safety— Researchers **must** implement clean air and layered protection mitigations to avoid reinfecting Long Covid research participants with SARS-CoV-2 or other airborne infections during study procedures. Research indicates that many research participants (including controls) have already been infected by Covid-19. Estimates from serology data showed that by the end of 2023, 87.2% of *all* Americans had been infected with Covid-19 at least once. [40] Unfortunately infection does not confer lasting immunity, and, more alarmingly, research has shown that the risk of Long Covid increases with repeat infections. [41] Many Long Covid patients report experiencing new damage with each reinfection, further diminishing their already-reduced baseline functioning.

Failure to implement mitigations and thereby exposing Long Covid research participants to Covid-19 and other pathogens is completely negligent. It also creates a confounding variable that distorts research results. Any infection resulting from non-existent or careless precautions during research trials should be reported to the appropriate research oversight board, and also noted in the research as an adverse event. [42]

Likewise, tests must be required on any blood/plasma products and organs used in treatments for SARS-CoV-2 just as is routinely done for HIV. This is necessary not only to avoid debilitating reinfections of Long Covid patients, but also to minimize confounding variables that could potentially jeopardize study results. Providing safer research environments increases the likelihood not only of more accurate study outcomes, but

also helps attract willing research candidates, both among Long Covid patients and Covid-negative controls (or “Novids”) who have worked hard for years at implementing personal mitigations in order to avoid infection.

10. Streamline treatment and clinical trial processes — Numerous roadblocks exist that slow progress for Long Covid researchers and clinicians, but streamlining certain processes is achievable to obtain faster public access to treatments and cures. One major obstacle is a surprising lack of cooperation from pharmaceutical companies. In attempting to conduct promising studies, researchers are frequently denied access to medications by the pharmaceutical manufacturers. In a 2025 article by Walrath, multiple Long Covid researchers spoke of their inability to obtain drugs from pharmaceutical companies including many monoclonal antibodies such as REGEN-COV, Pembrolizumab, Galcanezumab, Relatlimab and Nivolumab. [24] Incentivizing pharmaceutical companies to make drugs available for trials by Long Covid researchers and streamlining the processes to make this faster and easier would help speed research toward treatments and cures.

Another time-and cost-saving measure would be to expedite FDA approval of SARS-CoV-2 drugs approved for use in other countries. Examples include antivirals such as China’s Azvudine and Japan’s Ensitrelvir (Xocova).

Researchers face yet another challenge when attempting to access tissue samples and cadavers of Long Covid deceased. Establishing a program for people with Long Covid to designate donation of their bodies to science when they die would allow researchers in public and private sector labs to more easily receive these donations for use in studies to treat and move closer to a cure for Long Covid. [43]

11. Implement Emergency Use Authorizations (EUA)— declaring Long Covid a Public Health Emergency as well as a National Health Emergency is urgently needed to facilitate clinical trials and expedite distribution of treatments to patients. EUAs allow repurposing of drugs currently used to treat other conditions to also be used in treating Long Covid. The obvious benefit is that these medications have already been FDA approved, ensuring that they have passed a certain safety threshold.

Implementing a Public Health Emergency declaration for Long Covid can also allow use of other techniques and technologies. One particularly vital program enacted during the Covid Public Health Emergency was telemedicine. Many patients nationwide are unable to travel to access healthcare for a variety of reasons. This is particularly true for many of the sickest patients who have been disabled by Long Covid. Reestablishing the Public

Health Emergency and National Health Emergency programs are essential to speed treatment and cures to people all over the country.

12. Children and Adults as Research Participants— It's important that both children and adults participate in Long Covid clinical trials to evaluate potential treatments. When children aren't included in research studies, they do not benefit from potential treatments and cures. Because treatments for children require separate approval by the FDA, performing trials concurrently on pediatric patients will ensure that they can benefit more expeditiously than awaiting a separate trial. It is imperative that we make effective treatments and cures available to kids as soon as possible to safeguard our future generations, and to curtail infections and reinfections for kids and families.

13. Ensure that Treatment is Available for All Who Need It— Consideration should be given to ways of making treatments and cures more widely available. For example, participants in a clinical trial who are given a placebo should be guaranteed to receive the actual treatment at the end of a successful clinical trial, so that all participants who helped with the study receive the benefits from its success. Also, people who live far from research labs, National Institute of Health centers, or Long Covid treatment clinics should have the opportunity to participate in clinical trials and benefit from treatments and cures. This could be offered via telemedicine and/or through collaborations with local community healthcare providers .

14. Opportunistic Infections and Co-Infections— As with other persistent viruses, ongoing infection with the SARS-CoV-2 virus causes immune system damage. Such immune deficiency opens the door to other opportunistic infections such as mycoplasma pneumonia, tuberculosis, candida, fungal infections, and more. [44] [45] Covid can reactivate latent viruses and bacterial infections previously contracted by patients, such as CMV, VZV/shingles, EBV, Lyme, and tuberculosis. These opportunistic infections and co-infections must also be studied and treated so that everyone can benefit from treatments and cures for Long Covid.

Over 1 million Americans have died from the immediate effects of acute Covid, and thousands more have died from Long Covid. [2] It is vitally important that we act now to research, treat, and cure Long Covid. We can and should adopt these guidelines as a vital step toward effectively researching, treating, and ultimately curing Long Covid.

Note: LCAP-CURE has assembled a list of some of the most promising therapeutics that merit further study in the APPENDIX sections of this booklet.

New Models for Clinical Trials & Decision-Making for Long Covid

As discussed earlier, in order to assess effectiveness of any interventions, a reliable diagnostic biomarker test for Long Covid and a means to measure RNA viral load as well as immune changes are imperative to facilitate decision-making tools for trials and government committees. Currently there is no reliable, standardized method to accurately assess the effectiveness of any therapeutic intervention. To summarize, there are three primary challenges that need to be addressed:

- **Diagnostic Challenge:** A definitive diagnostic test is crucial to:
 - o Rule out other conditions that may mimic Long Covid symptoms.
 - o Ensure that research participants are accurately diagnosed with Long Covid.
- **RNA Viral Load and Immune Test Challenge:**
 - o Quantifying viral load and immune changes, using both transcriptomic and proteomic tools, is essential to understand the disease's progression and to objectively measure the impact of potential treatments.
 - o This data is critical for determining whether a therapeutic intervention effectively reduces viral persistence, a key diagnostic factor in Long Covid.
- **Long Covid Resistance Panels:**
 - o Adapting a HIV type resistance panel model for SARS-CoV-2, including whole blood transcriptomic analysis, can significantly improve the management of Long Covid and save lives. This approach not only identifies resistance mutations but also provides insights into the patient's immune response, enabling a more personalized and effective treatment strategy. As SARS-CoV-2 continues to evolve, resistance testing using genotypic whole blood transcriptomics and phenotypic testing will play an increasingly crucial role for Long Covid patient outcomes.

Recommended Approach For Evaluating Potential Treatments:

LCAP-CURE recommends the prioritization of evaluating medications with antiviral properties for their potential efficacy in treating Long Covid. We are proposing evaluation of a subset of preexisting antivirals and monoclonal antibodies as well as medications with immune modulating and antiviral properties, some of which are currently in clinical trials (see APPENDIX A: Antivirals). This approach is based on the

growing evidence that SARS-CoV-2 viral infection plays a significant role in the development and continuation of Long Covid symptoms.

It is imperative that research avoids two pitfalls in trialing medications:

- **Designing clinical trials that are too short**
 - Antivirals can require months of consistent and continuous use before improvement can be measured.
 - Short-term trials of medications can lead to drug resistance, in effect disqualifying a patient from re-trialing a drug for the appropriate amount of time.
- **Studying treatments as monotherapies**
 - Just as effective HIV treatment requires a combination of antivirals, treating Long Covid requires a multi-pronged approach. This strategy is essential to combat viral persistence, enhance drug effectiveness, and minimize the risk of drug resistance. Monotherapy will not suffice.
 - Adding SARS-CoV-2 monoclonal or polyclonal antibodies to a treatment regimen in tandem with antivirals can reduce the detectable RNA viral load in patients. [46]

Recommendations for Assessing Clinical Trials Going Forward:

1. **Prioritize Diagnostic Development:** Invest in the development and validation of a sensitive and specific diagnostic biomarker test for Long Covid. We are stressing a high priority for the two Long Covid biomarkers Antisense RNA and FYN. Both were discovered in the Belgium whole blood transcriptomic analysis study and are currently being validated at the time of this version's publication.
2. **Establish RNA Viral Load Measurement:** Develop and implement standardized methods for measuring RNA viral load in individuals with suspected Long Covid, using both transcriptomic and proteomic whole blood testing in addition to any other available tests.
3. **Focus on Antiviral, Monoclonal Antibody and Polyclonal Antibody Therapies:** Investigate antiviral therapies, both alone and in combination with other medications (such as monoclonal antibodies), as potential first-line treatments for Long Covid.
4. **Combination Therapies:** Explore combination therapies to address the complex nature of Long Covid and enhance treatment outcomes.

Past Disasters: How Unmet Criteria Wastes Long Covid Resources

Few proposed treatments for Long Covid have been tested in formal clinical trials, and ones that have been trialed unfortunately show underwhelming or conflicting results. It is crucial to test potential treatments in well-designed, ethical, and efficient clinical trials. For Long Covid, this means:

- Clearly defining the trial cohort with objective measures used for selecting study participants.
- Understanding the mechanism of the proposed drug and how it applies to the cohort.
- Having objective measures of trial endpoints and treatment efficacy.
- Facilitating a representative sample of Long Covid patients; for example, including those of different severity levels, disease progression, and where possible, patients with common comorbidities.
- Avoiding active ingredients as “placebos” unless trial is intended to compare potential treatments.
- Avoiding “standard of care” placebo arms when there is no current standard of care.
- Ensuring trial data is not corrupted by implementing mitigations to avoid Covid infections among research participants and ensure reporting of re-infection and/or exposure to SARS-CoV-2 or other infectious agents so that this influence can be reflected in research data.
- Promptly sharing trial data including endpoints and outcomes in a publicly accessible format.
- Having a plan for follow-through to validate and bring therapeutics to market when positive results are obtained.
- Sharing information via communication between research teams striving to replicate or build on another’s work with data that can be evaluated by direct comparison to the greatest extent possible.

Valuable time and research funding have been wasted as a result of failure to meet these criteria. Following are several examples of clinical trials which unfortunately squandered precious resources without providing meaningful development toward treatments. We hope these serve as lessons learned:

Ampligen (Rintatolod)— Ampligen is a selective TLR3 agonist that activates the innate immune system and promotes interferon production. It has been suggested for a wide

range of conditions, from cancer and ME/CFS to HIV/AIDS and H5N1 influenza, but has not been approved for any use in the United States due to poor trial designs. The same issues that caused early trials for use in HIV to be rejected by the FDA in the 1980s— database discrepancies, statistical analysis plans that were inconsistent with protocols, lack of dosing ranges, clinical pharmacology, and carcinogenicity data— have hampered efforts to trial the drug for use as an ME/CFS treatment in recent years. This also appears to be the reason the long-concluded trial for use as a Long Covid treatment has not been published beyond raw data results. Further confusing the issue, this study was a double-blind placebo controlled trial but not designed to determine statistical significance of improvement vs placebo. [47] This drug STILL needs urgent research conducted by independent teams possessing a strong clinical trial history who are not financially invested in the success or failure of this product.

BC007 (Rovunaptabin)— This drug is a thrombin binding aptamer that behaves in a similar way to an antibody to neutralize functional autoantibodies. While early studies showed promise, a larger scale placebo-controlled trial was never reported beyond a press release from the company stating no significant difference was found compared to placebo. However, an independent team *did* find significant improvement compared to placebo both across groups and longitudinally per individuals in a crossover study design. That team suggested that inclusion criteria and differences in trial flow and endpoints may be the reason for the disparities. [48] This highlights the urgent need for researchers to try to build on one another's work instead of producing large volumes of conflicting data that cannot be directly compared. It is also important to note that inclusion criteria for both teams in this particular study used an objective test (blood test for functional autoantibodies) to determine who might benefit from the proposed treatment's mechanism— a point the vast majority of trials to date for all proposed treatments have lacked.

Leronlimab— Leronlimab is a monoclonal antibody that directly binds to expressed CCR5 on cell surfaces. It was trialed in a small number of Long Covid patients in a double-blind, placebo-controlled trial published in April 2022 with favorable symptom score results, but to date no follow-up with larger cohorts has been initiated and no long-term follow-up of patients has been conducted.[49] This may owe to the fact that, while endpoints were met, their mechanism was paradoxically opposite to the initial hypothesis. Further exploration of this promising treatment is long overdue.

Selzentry (Maraviroc)— Maraviroc is an oral CCR5 antagonist widely used for HIV treatment. It was trialed in conjunction with pravastatin in 2021 in a small-scale, open-label study with the proposed mechanism of targeting chronic immune activation via monocyte-endothelial-platelet axis. Favorable results were posted as a preprint in

February 2022, but again, no follow-up has been done nor have the results been peer reviewed. [50] Despite this, the group responsible for the study has continued to recommend this treatment to patients meeting certain clinical criteria, with anecdotally favorable results. Urgent follow up is needed for this potential treatment option.

LDN (Low Dose Naltrexone)— Naltrexone is a nonspecific opioid antagonist that, at low doses, stimulates endogenous opioid and opioid receptor expression and modulates the immune response by inhibiting T and B cell proliferation and blocking inflammatory cytokine production downstream of TLR4 signaling. LDN has been widely used off-label for these purposes in autoimmune and post-acute viral illnesses and many Long Covid patients report improvement. However, most studies have been retrospective, with varying dosages between patients, making data comparison difficult. Further, in nearly all cases, the studies were open label and did not have a control arm. One small-scale placebo controlled study found significant improvement in fatigue, however there was no long term followup of patients after discontinuation of the drug. [51] [52] Further exploration of this potential candidate is needed.

Paxlovid (Nirmatrelvir /Ritonavir)— Paxlovid contains a 3CL main protease inhibitor for SARS-CoV-2, and the HIV protease inhibitor ritonavir as an agent to boost bioavailability of Nirmatrelvir. It is approved for use in acute infection when started within five days of symptoms. The only published trial results to date which tested for efficacy against Long Covid showed no difference in symptom score improvement between those given Paxlovid, or those receiving Ritonavir as a placebo. This is problematic because Ritonavir is an active component of the study drug, and has alone been demonstrated to inhibit SARS-CoV-2 in vitro. While this has been presented as evidence against viral persistence, further trials with the same poor design are currently underway while other, more promising drugs are ignored. [53] [54] Further complicating interpretation of results, the only metric used to gauge efficacy were subjective symptom questionnaires. This is problematic because for many Long Covid patients, the nature of this illness can cause fluctuating symptoms. It is imperative that poor trial design not be allowed to misguide future research decisions.

Conclusion:

In this publication, we have identified key problems in Long Covid research and treatment. These are solvable problems. The ongoing impact of Long Covid on individuals and society demands urgent action. The "let it rip" approach to COVID-19 has resulted in millions of deaths and far too many people suffering from the fatal and debilitating long-term health consequences of Long Covid. Without effective treatments and research approaches in place to address the disease. We urge those at HHS, CDC,

FDA, NIH, the U.S. Senate HELP Committee, and all health authorities and scientists involved in Long Covid research to prioritize implementing the 14 principles and recommendations outlined in this publication. We will not rest until this is done.

Our health, safety, economic stability, national security as well as our children's future depends on addressing this threat to the wellbeing of our country.

APPENDIX:

LCAP-CURE has analyzed research articles and news coverage to compile a list of therapeutics that seem the most promising to address viral persistence and replication, the key drivers of Long Covid. LCAP-CURE has cast a wide net in compiling this list of therapeutics we believe deserve more research. Our medication list consists of drugs currently on the market to treat other conditions, drugs currently undergoing clinical trials, and drugs for which trials have not yet begun. Each of the medications listed have antiviral properties, or are immune modulating drugs, or are other drugs of interest such as biologics, including monoclonal antibodies, polyclonal antibodies, and immunoglobulins. In total, LCAP-Cure is submitting 21 antivirals, 14 biologics, and 20 other drugs for a total of 55 drugs *so far* for consideration by the NIH. LCAP-CURE will be submitting each of these through the NIH RECOVER-TLC portal and will continue to update, revise, and add to this list of drugs.

APPENDIX A: Antivirals

Abacavir (Ziagen)— Nucleoside analog reverse transcriptase inhibitor.

Recommended uses would be in combination therapeutics.

Stage of overall development: Approved for another indication.

Symptoms/Syndromes aims to target: SARS-CoV-2 viral persistence.

URLs:

Copertino 2020 <https://www.tandfonline.com/doi/full/10.1080/07391102.2021.1901144>

Alavian 2020 <https://pmc.ncbi.nlm.nih.gov/articles/PMC7753707/>

Tomic 2021 <https://www.sciencedirect.com/science/article/pii/S2352914821000198>

Atazanavir (Reyataz)— Biomed's azapeptide antiretroviral protease inhibitor used to treat HIV AIDS infection; inhibits the enzyme UDP glucuronosyltransferase (UGT) 1A1.

Stage of overall development: Approved for another indication.

Symptoms/Syndromes intervention aims to target: inhibit the viral replication cycle of SARS-CoV-2 by binding the main protease inhibitor.

URLs:

Brazil Clinical Trial 2021 <https://clinicaltrials.gov/study/NCT04468087>

Biomed Clinical Trial 2022 <https://clinicaltrials.gov/study/NCT04452565>

Copertino Jr. 2021

<https://www.tandfonline.com/doi/full/10.1080/07391102.2021.1901144#d1e392>

Azvudine— Chinese antiviral used in acute COVID. Nucleoside analog inhibitor of RdRp. aims to target: Reduction of SARS-CoV-2 viral load.

Stage of overall development: Approved for another indication.

Symptoms/Syndromes intervention aims to target: neutralizing activity against SARS-CoV-2.

URLs:

Phase 3 Clinical Trial 2022 <https://clinicaltrials.gov/study/NCT05033145>

Phase 3 Clinical Trial 2021 <https://clinicaltrials.gov/study/NCT04668235>

Dian 2023 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10188372/>

Zhou 2024

<https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-023-08944-z>

Chen 2023 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10559905/>

Bictegravir (GS-9883)— Gilead's integrase strand transfer inhibitor and antiretroviral medication used to treat HIV infection when used as part of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide).

Stage of overall development: Approved for another indication.

Aims to target: neutralize SARS-CoV-2 virus.

URLs:

Oner et al 2023 <https://pubmed.ncbi.nlm.nih.gov/37545919/>

Dhaka et al. 2023 <https://www.biorxiv.org/content/10.1101/2022.03.12.484092v4>

Dolutegravir (Tivicay/GSK-572/S-349572)— ViiV Healthcare's antiretroviral integrase inhibitor.

Stage of overall development: Approved for another indication.

Symptoms/Syndromes intervention aims to target: increase CD4+ T cell count.

URLs:

Erukainure, 2024 <https://pmc.ncbi.nlm.nih.gov/articles/PMC11626820/>

Buzon 2023 <https://pmc.ncbi.nlm.nih.gov/articles/PMC9963008/>

Elvitegravir (Vitekta)—Gilead's antiretroviral integrase strand transfer inhibitor used to treat HIV/AIDS.

Stage of overall development: Approved for another indication.

Aims to target: decreasing SARS-CoV-2 viral replication and increasing CD4 counts.

URLs:

Zhou et al., 2020

<https://www.sciencedirect.com/science/article/pii/S0888754320307813>

Salari et al. 2022

<https://www.benthamdirect.com/content/journals/aia/10.2174/2211352519666210928110627>

Ensitrelvir (Xocova S-217622)— Shionogi's antiviral post-exposure prophylaxis for acute COVID. 3CL protease inhibitor.

Stage of overall development: Phase 2/3.

Symptoms/Syndromes intervention aims to target: Reduction of SARS-CoV-2 viral load & inflammation.

URLs:

UCSF Clinical Trial <https://clinicaltrials.gov/study/NCT06161688>

Yotsuyanagi Sep 2024

<https://www.sciencedirect.com/science/article/pii/S0166354224001670>

Yotsuyanagi Feb 2024 <https://europepmc.org/article/MED/38335000>

Yamato 2024 <https://pubmed.ncbi.nlm.nih.gov/38367932/>

Favipiravir (Avigan)— Toyama Chemical's pyrazinecarboxamide-derived nucleoside analogue RNA dependent RNA polymerase inhibitor that is approved for treatment of influenza in Japan.

Stage of Overall Development: Phase 2/3.

Aims to target: reducing SARS-CoV-2 viral load.

URLs:

Stanford Phase 2 Clinical Trial <https://clinicaltrials.gov/study/NCT04346628>

Turkey 2020 Clinical Trial

<https://clinicaltrials.gov/study/NCT04645433>

2021 Russia Phase 3 Clinical Trial <https://clinicaltrials.gov/study/NCT05185284>

Siripongboonsitti et al. 2023 <https://www.nature.com/articles/s41598-023-42195-x>

Shah et al. 2023

[https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(22\)00412-X/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(22)00412-X/fulltext)

Ibuzatrelvir (PF-07817883)— Pfizer's oral SARS-CoV-2 main protease (Mpro) inhibitor.

Stage of overall development: Phase 2/3.

Symptoms/Syndromes aims to target: Reduction of SARS-CoV-2 viral load and inhibiting SARS-CoV-2 viral replication.

URLs:

Pfizer Phase 3 Clinical Trial <https://clinicaltrials.gov/study/NCT06679140>

Mortezavi 2024

<https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciae529/7863440>

Brewitz 2024 <https://pubmed.ncbi.nlm.nih.gov/38967233/>

Pfizer

<https://pfizermedical.pfizerpro.com/api/vc/en/medical/assets/0f98ccb4-08bb-46d6-abfe-3a89b62dc8fc/Ibuzatrelvir%20Phase%20b%20Study%20results-updated%20poster%20%281%29.pdf>

Indinavir (Crixivan)— Merck's small molecule antiretroviral protease inhibitor used to treat HIV AIDS.

Stage of overall development: Approved for another indication.

Symptoms/Syndromes aims to target: reduce viral load and inhibit the viral replication cycle of SARS-CoV-2 by binding the main protease inhibitor.

URLs:

Indu et al., 2020 <https://pmc.ncbi.nlm.nih.gov/articles/PMC7587076/>

Copertino Jr. 2021

<https://www.tandfonline.com/doi/full/10.1080/07391102.2021.1901144#d1e392>

Lenacapavir (Sunlenca)— Gilead antiretroviral for HIV/AIDS that rigidifies HIV's capsid protein protecting the virus's RNA, which blocks transmission of the virus.

May have potential against other viruses such as SARS-CoV-2 (even the prevention or reduction of reinfections would help people with Long Covid).

Stage of overall development: Approved for another indication.

Symptoms/Syndromes intervention aims to target: Reduction of SARS-CoV-2 viral load; reduction of SARS-CoV-2 reinfection potential.

URLs:

Erukainure 2024 <https://pmc.ncbi.nlm.nih.gov/articles/PMC11626820/>

Kelley 2024 <https://www.nejm.org/doi/full/10.1056/NEJMoa2411858>

Lopinavir (ABT-378)— protease inhibitor antiretroviral which has been tested in combination therapies (Lopinavir–Ritonavir, and Lopinavir–Ritonavir–Ribavirin); used for treating HIV/AIDS.

Stage of overall development: Approved for another indication.

Aims to target: reducing SARS-CoV-2 viral load.

URLs:

U of Washington Phase 2/3 Clinical Trial 2020

<https://clinicaltrials.gov/study/NCT04354428>

Qatar Clinical Trial 2020 <https://clinicaltrials.gov/study/NCT04425382>

Lebanon 2020 Clinical Trial <https://clinicaltrials.gov/study/NCT04645433>
Recovery Collaborative Group 2020
<https://pmc.ncbi.nlm.nih.gov/articles/PMC7535623/>
Elmekaty 2022 <https://pmc.ncbi.nlm.nih.gov/articles/PMC9067693/>
Hung 2020 et al.
[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31042-4/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31042-4/fulltext)

Maraviroc (Selzentry)— Chemokine receptor (CCR5) antagonist that acts against HIV by blocking cellular entry. Has been used in Long Covid protocols, with demonstrated clinical improvements.

Stage of overall development: Approved for another indication.

Symptoms/Syndromes aims to target: SARS-CoV-2 viral persistence.

URLs:

Mt Sinai Clinical Trial 2024 <https://clinicaltrials.gov/study/NCT06511063>

Patterson 2023 <https://pubmed.ncbi.nlm.nih.gov/36844201/>

Obeldesivir (GS-5245/ATV006)— Gilead's small molecule oral antiviral (an oral remdesivir analogue).

Stage of overall development: Phase 2/3.

Symptoms/Syndromes aims to target: Reduction of SARS-CoV-2 viral RNA and inhibiting SARS-CoV-2 replication.

URLs:

Gilead OAKTREE trial 2024 <https://clinicaltrials.gov/study/NCT05715528>

Gilead BIRCH clinical trial 2024 <https://clinicaltrials.gov/study/NCT05603143>

UNC 2024

<https://sph.unc.edu/sph-news/oral-nucleoside-antiviral-is-progressing-toward-future-pandemic-preparedness/>

Gilead 2024

[https://www.askgileadmedical.com/docs/conference/2024_IDWeek_COVID_ODV_P92](https://www.askgileadmedical.com/docs/conference/2024_IDWeek_COVID_ODV_P92_Rodriguez_BIRCHTiterOral_FINAL@pdf)

[Rodriguez BIRCHTiterOral FINAL@pdf](https://www.askgileadmedical.com/docs/conference/2024_IDWeek_COVID_ODV_P92_Rodriguez_BIRCHTiterOral_FINAL@pdf)

Sofosbuvir and its various combination formulations (e.g., ledipasvir-sofosbuvir [Harvoni])— Hepatitis C antiviral with demonstrated effectiveness against acute COVID. Nucleotide analog inhibitor RdRp with stronger binding affinity for SARS-CoV-2 RdRp than tenofovir. Additionally, novel derivatives of sofosbuvir should be tested as several have been shown to have even stronger binding affinity for SARS-CoV-2.

Stage of overall development: Approved for another indication.

Symptoms/Syndromes aims to target: SARS-CoV-2 viral persistence.

URLs:

Elgohary 2022 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9015168/>
Alrehaily 2023 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10754943/>
Hsu 2022 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8817946/>
Abbass 2021 <https://pubmed.ncbi.nlm.nih.gov/34379337/>

S-892216— Shionogi 3CL protease inhibitor developed through the Rapid Response Partnership Vehicle (RRPV) under the Biomedical Advanced Research and Development Authority (BARDA) as a pre-exposure prophylactic for COVID-19. Stage of overall development: Preclinical.

Symptoms/Syndromes aims to target: Reduction of SARS-CoV-2 viral load by blocking the main protease (Mpro) of the SARS-CoV-2 virus, preventing its replication within cells; reduction of SARS-CoV-2 reinfection potential.

URLs:

Pharmaceutical Technology 2025

<https://www.pharmaceutical-technology.com/news/shionogi-awarded-375m-from-hs-for-preventative-covid-19-injectable/>

Clinical Trial Vanguard 2025

<https://www.clinicaltrialvanguard.com/news/shionogis-s-892216-breakthrough-covid-19-antiviral-for-at-risk-groups/>

STRIBILD (elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate)— An antiretroviral combination therapy used as post-exposure prophylaxis for HIV and for treatment of HIV. Also effective against EBV reactivation and Hepatitis B. STRIBILD contains the drugs in Truvada plus cobicistat (a booster that increases levels of antivirals in the body) and elvitegravir (an integrase inhibitor).

Stage of overall development: Approved for another indication.

Symptoms/Syndromes intervention aims to target: SARS-CoV-2 viral persistence.

URLs:

Mt Sinai 2024 <https://clinicaltrials.gov/study/NCT06511063>

UCSF 2022

<https://pmc.ncbi.nlm.nih.gov/articles/PMC8243808/#:~:text=PWH%20taking%20ART,-1,supporting%20the%20possibility%20of%20confounding>

Luca Shytaj 2022 <https://outbreak.info/resources/pmid35229634>

AAAS 2023 <https://www.eurekalert.org/news-releases/1010145>

ISS Italy 2022

https://www.iss.it/en/covid-19-primo-piano/-/asset_publisher/yX1afjCDBkWH/content/covid-19-farmaco-anti-hiv-potrebbe-essere-efficace-contro-l-infezione-da-sars-cov-2

Alexpandi 2020 <https://pubmed.ncbi.nlm.nih.gov/32793181/>

TDI-015051— Tuschi Lab's small molecule inhibitor of the viral guanine-N7 methyltransferase (MTase) NSP14.

Stage of overall development: Preclinical.

Symptoms/Syndromes aims to target: Neutralize SARS-CoV-2 by interfering with the viral methyltransferase enzyme NSP14 and preventing SARS-CoV-2 viral replication.

URLs:

Meyer 2024 <https://www.nature.com/articles/s41586-024-08320-0>

Halford 2024

<https://cen.acs.org/pharmaceuticals/drug-discovery/new-way-take-down-SARS/102/web/2024/12>

SciTech Daily 2024

<https://scitechdaily.com/beyond-paxlovid-scientists-unveil-game-changing-antiviral-that-could-combat-covid-ebola-and-more/>

Truvada (emtricitabine and tenofovir disoproxil fumarate)— Antiretroviral combination therapy used as pre-exposure prophylaxis for HIV and for treatment of Hepatitis B. Also effective against EBV reactivation.

Stage of overall development: Approved for another indication.

Symptoms/Syndromes intervention aims to target: SARS-CoV-2 viral persistence.

URLs:

Nov 2024 Clinical Trial

<https://clinicaltrials.gov/study/NCT06511063?cond=long%20covid&intr=truvada&rank=1>

Jul 2022

<https://pmc.ncbi.nlm.nih.gov/articles/PMC8243808/#:~:text=PWH%20taking%20ART,-1,supporting%20the%20possibility%20of%20confounding>

VV116 (Deuremidevir)— A Chinese-developed Remdesivir derivative and RNA-dependent RNA polymerase inhibitor that has shown efficacy in the treatment of acute COVID and resulted in less viral load and symptom rebound after treatment for acute COVID-19 than nirmatrelvir-ritonavir. First described in November 2020 by a team from Wuhan Institute of Virology and Vigonvita. Available as oral tablets.

Stage of Overall Development: Phase 2/3.

Symptoms/Syndromes intervention aims to target: SARS-CoV-2 viral persistence.

URLs:

Fan 2024

[https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(23\)00577-7/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(23)00577-7/fulltext)

Yang 2024

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2816033#google_vignette

WEHI-P8 — Coronaviral protease PLpro inhibitor in the WEHI-P series.

Stage of Overall Development: Preclinical.

Symptoms/Syndromes aims to target: reduce the levels of pro-inflammatory cytokines in the lungs; reduce neuroinflammation in the brain.

URLs:

Komander 2024 <https://www.researchsquare.com/article/rs-4899442/v1>

APPENDIX B: Monoclonal and Polyclonal Antibodies

5B8 (MA5-33374) — Invitrogen's OSCAR anti-fibrin monoclonal antibody

Stage of overall development: Preclinical

Symptoms/Syndromes aims to target: binding the CD11b receptor involved in immune activation to inhibit the fibrin-spike interaction, mitigating clot formation and inflammation

URLs:

Malesu 2024

<https://www.news-medical.net/news/20240829/Fibrin-fuels-thromboinflammation-and-brain-damage-in-COVID-19.aspx>

Ryu 2024 <https://www.nature.com/articles/s41586-024-07873-4>

AER002 - (P2G3) — Fully human monoclonal antibody and anti-endothelin receptor B antibody.

Stage of overall development: Phase 2.

Symptoms/Syndromes aims to target: reducing SARS-CoV-2 viral persistence in patients with Long Covid.

URLs:

Peluso Clinical Trial 2023 Phase 2 <https://clinicaltrials.gov/study/NCT05877508>

Moullan 2024 <https://pmc.ncbi.nlm.nih.gov/articles/PMC10828317>

Bamlanivimab and Etesevimab (LY-CoV016/JS016) — Combination of two human recombinant neutralizing IgG1-kappa monoclonal antibodies.

Stage of overall development: Approved for another indication.

Symptoms/Syndromes aims to target: reducing SARS-CoV-2 viral load and improving clinical outcomes.

URLs:

U. Pitt trial 2022 <https://clinicaltrials.gov/study/NCT04790786>

Italian trial 2022 <https://clinicaltrials.gov/study/NCT05268601>

Canada Trial 2022 <https://clinicaltrials.gov/study/NCT04748588>

Gunaratne 2021 <https://pmc.ncbi.nlm.nih.gov/articles/PMC8384088/>

Prior EUA 2021-2023 <https://www.fda.gov/media/145802/download>

Casirivimab & Imdevimab (Regeneron/REGEN-COV/Ronapreve/REGN10933 and REGN10987)— Combination of two recombinant human IgG1 monoclonal antibodies.

Stage of overall development: Approved for another indication.

Symptoms/Syndromes aims to target: decreasing overall infection rates and reducing SARS-CoV-2 viral load.

URLs:

USA trial <https://clinicaltrials.gov/study/NCT04992273>

Canada trial <https://clinicaltrials.gov/study/NCT04748588>

Italy trial <https://clinicaltrials.gov/study/NCT05268601>

Dutch trial <https://clinicaltrials.gov/study/NCT05195060>

Gunaratne 2021 <https://pmc.ncbi.nlm.nih.gov/articles/PMC8384088/>

Leronlimab (PRO 140) – Humanized IgG4 monoclonal antibody that blocks C–C chemokine receptor type 5.

Aims to target: cytokine storm and normalize CD4/CD8 ratios.

CytoDyn Clinical Trial Phase 2b/3 2020 <https://clinicaltrials.gov/study/NCT04347239>

CytoDyn Phase 2 Clinical Trial 2020 <https://clinicaltrials.gov/study/NCT04343651>

Seethamraju et al. (2024)

[https://www.clinicaltherapeutics.com/article/S0149-2918\(24\)00260-1/abstract](https://www.clinicaltherapeutics.com/article/S0149-2918(24)00260-1/abstract)

Agresti et al. 2021 <https://pmc.ncbi.nlm.nih.gov/articles/PMC7823045/>

Ofatumumab (Kesimpta/Arzerra)— Anti-CD20 monoclonal antibody.

Stage of overall development: Approved for another indication.

Symptoms/Syndromes aims to target: improving immune response to SARS-CoV-2.

URLs:

Novartis Clinical Trial 2024 stage 4 <https://clinicaltrials.gov/study/NCT04869358>

Wang 2024 <https://onlinelibrary.wiley.com/doi/10.1002/acn3.52284>

Cross 2022 <https://pmc.ncbi.nlm.nih.gov/articles/PMC8918079/>

Pemivibart (Pemgarda/VYD222)— Human monoclonal antibody with neutralizing activity against major SARS-CoV-2 variants.

Stage of overall development: Approved for another indication.

Symptoms/Syndromes aims to target: neutralizing major SARS-CoV-2 variants, including JN.1.

URLs:

Invyvid Phase II Clinical Trial 2024 <https://clinicaltrials.gov/study/NCT06039449>

Authorized under EUA Aug 2024 pre-exposure prophylaxis to help prevent COVID-19
<https://www.fda.gov/drugs/emergency-preparedness-drugs/emergency-use-authorizations-drugs-and-non-vaccine-biological-products>

Regdanvimab (Regkirona/CT-P59)— Human monoclonal antibody with neutralizing activity against SARS-CoV-2.

Stage of overall development: Approved for another indication.

Symptoms/Syndromes aims to target: neutralizing SARS-CoV-2 and reducing viral load.

URLs:

Celltrion Phase 2/3 Clinical Trial <https://clinicaltrials.gov/study/NCT04602000>

French Clinical Trial 2022 <https://clinicaltrials.gov/study/NCT05439044>

EU Authorization 2021

<https://www.ema.europa.eu/en/medicines/human/EPAR/regkirona> Jang 2023

<https://pmc.ncbi.nlm.nih.gov/articles/PMC9822548/>

SA55 (BD55-5514)— Fully humanized monoclonal antibody with neutralizing activity against SARS-CoV-1 & SARS-CoV-2.

Stage of overall development: Phase 2.

Symptoms/Syndromes aims to target: neutralizing SARS-CoV-2 & reducing viral load.

URLs:

Sinovac Phase I Clinical Trial 2023 <https://clinicaltrials.gov/study/NCT06048393>

Sinovac Phase II Clinical Trial 2024 <https://clinicaltrials.gov/study/NCT06042764>

Cao 2022 <https://www.sciencedirect.com/science/article/pii/S2211124722017375>

Sipavibart (Kavigale/AZD3152/Evusheld 2) — RQ Bio and AstraZeneca's monoclonal antibody with neutralizing activity against SARS-CoV-2.

Stage of overall development: Phase 2/3.

Symptoms/Syndromes aims to target: neutralizing SARS-CoV-2 virus.

URLs:

AstraZeneca Clinical Trial Phase 2/3 <https://clinicaltrials.gov/study/NCT05648110>

AstraZeneca Clinical Trial 2023 <https://clinicaltrials.gov/study/NCT05872958>

AstraZeneca Clinical Trial Phase I <https://clinicaltrials.gov/study/NCT0593264>

AstraZeneca Phase 3

<https://www.astrazeneca.com/media-centre/press-releases/2024/supernova-trial-meet-covid-19-prevention-endpoint.html>

EU Authorization

https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-kavigale_en.pdf

Sotrovimab/Xevudy (VIR-7831/GSK4182136) — Vir's human monoclonal antibody with neutralizing activity against SARS-CoV-2.

Stage of overall development: Approved for another indication.

Symptoms/Syndromes aims to target: neutralizing SARS-CoV-2.

URLs:

VIR Phase 3 clinical trial 2023 <https://clinicaltrials.gov/study/NCT04913675>

US Phase 2 Trial 2023 <https://clinicaltrials.gov/study/NCT05210101>

US Trial at UWash Phase 1 2022 <https://clinicaltrials.gov/study/NCT05135650>

Prior EUA 2022

<https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-sotrovimab-emergency-use-authorization>

Tixagevimab/Cilgavimab — AstraZeneca's Evusheld (AZD7442, combining AZD8895/AZD1061) - a combination of two human monoclonal antibodies with neutralizing activity against SARS-CoV-2.

Stage of overall development: Approved for another indication.

Symptoms/Syndromes aims to target: neutralizing SARS-CoV-2.

URLs:

AstraZeneca Phase 4 Clinical Trial 2023 <https://clinicaltrials.gov/study/NCT05569408>
Lancet 2022

[https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(22\)00215-6/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(22)00215-6/fulltext)
Science Translational Medicine 2022

<https://www.science.org/doi/10.1126/scitranslmed.abl8124>

Vilobelimab (IFX-1/Gohibic) — InflaRx NV's chimeric IgG4 anti-C5a monoclonal antibody which blocks C5a as a key "amplifier" of the inflammatory response driving tissue and organ damage.

Stage of overall development: Approved for another indication.

Symptoms/Syndromes aims to target: control the inflammatory response driving tissue and organ damage by blocking C5a as a key "amplifier" of this response.

URLs:

Clinical Trial 2023 <https://clinicaltrials.gov/study/NCT04333420>

Vlaar 2022 <https://pmc.ncbi.nlm.nih.gov/articles/PMC9451499/>

EUA 2023

<https://www.fda.gov/drugs/drug-safety-and-availability/fda-authorizes-gohibic-vilobelimab-injection-treatment-covid-19>

VIR-7229— Vir Biotechnology’s human IgG1-kappa SARS-CoV-2 receptor binding domain-targeting monoclonal antibody.
Stage of overall development: Preclinical.
Symptoms/Syndromes aims to target: neutralizing SARS-CoV-2 & reducing viral load.
URLs: Rosen 2024 <https://pmc.ncbi.nlm.nih.gov/articles/PMC11645210/>

APPENDIX C: OTHER DRUG TREATMENTS

Ampligen (Rintatolod)— Aim Immunotech’s immunomodulatory double-stranded RNA molecule, TLR3 agonist, activates TLR3 inducing innate immune responses.
Symptoms/Syndromes aims to target: block viral replication.
Stage of overall development: Phase 2.
URLs:
AIM Immunotech 2023 Phase 2 Clinical Trial
<https://clinicaltrials.gov/study/NCT05592418>
Mustafa et al. 2021 <https://pmc.ncbi.nlm.nih.gov/articles/PMC8227153/>
Hohberger 2024 et al. <https://www.medrxiv.org/content/10.1101/2024.12.13.24318856v1>

Anakinra (Kineret by Swedish Orphan Biovitrum)— Immunosuppressant interleukin-1 receptor antagonist protein that blocks immune processes leading to inflammation following SARS-CoV-2 infection.
Stage of overall development: Approved for another indication.
Aims to target: Reduction of inflammation in SARS-CoV-2.
URLs:
Phase 2 Clinical Trial 2023 <https://clinicaltrials.gov/study/NCT05926505>
Phase 2/3 Clinical Trial 2023 <https://clinicaltrials.gov/study/NCT04443881>
Phase 3 Clinical Trial U. Oxford <https://clinicaltrials.gov/study/NCT0438>
UVa study
<https://www.news-medical.net/news/20240906/Arthritis-medications-could-reverse-COVID-lung-damage.aspx#>

Baricitinib (Eli Lilly and Incyte’s Olumiant)— Janus kinase (JAK) inhibitor.
Stage of overall development: Approved for another indication.
Aims to target: Reduction of systemic and neuroinflammation.
URLs:
REMAP-CAP Phase 3 Clinical Trial <https://clinicaltrials.gov/study/NCT02735707>

ACTT NIAID Phase 3 Clinical Trial <https://clinicaltrials.gov/study/NCT04401579>
ACTT-4 Phase 3 Clinical Trial <https://clinicaltrials.gov/study/NCT04640168>)
Vanderbilt study
<https://reporter.nih.gov/search/0ILh2B2lSUybBDyu43zYtQ/project-details/10827260>

B11-E8-F3— Trivale engineered nanobody with three nanobodies joined tandemly in trivalent form (SN-F3, ZF-B11 and ZF-E8) with antiviral activity against SARS-CoV-1 and SARS-CoV-2.

Stage of overall development: Preclinical.

Aims to target: neutralize SARS-CoV-2 and reduce SARS-CoV-2 viral load.

URLs:

Wang 2024 <https://onlinelibrary.wiley.com/doi/10.1002/adv.202402975>

B13-B13-B13— Multivalent trimeric homotrimer engineered nanobody with neutralization activity against SARS-CoV-2.

Stage of overall development: Preclinical.

Aims to target: neutralizing SARS-CoV-2.

URLs:

Wang 2024 <https://onlinelibrary.wiley.com/doi/10.1002/adv.202402975>

BC-007 (Rovunaptabin)— German drug that neutralizes functional autoantibodies against G-protein coupled receptors, which disrupt normal cellular functions by binding to cell receptors or other proteins, often imitating or blocking natural signals and resulting in a variety of autoimmune diseases. Administered by infusion.

Developed for treatment of heart failure, with publication documenting safety & efficacy.

Stage of overall development: Phase 2/3.

Aims to target: neutralize functional autoantibodies against G-protein coupled receptors, which disrupt normal cellular functions by binding to cell receptors or other proteins.

URLs:

Clinical Trials 2024 <https://clinicaltrials.gov/study/NCT05911009>

Hohberger 2024 Phase 2a clinical trial results preprint:

<https://www.medrxiv.org/content/10.1101/2024.12.13.24318856v1.full.pdf>

Cefuroxime (Zinacef/Ceftin)— Cephalosporin small molecule antibiotic with antiviral action that inhibits 3 main proteins (protease, RNA dependent polymerase and ACE2 spike complex).

Stage of overall development: Approved for another indication.

Aims to target: antiviral action against SARS-CoV-2 viral persistence.

URLs:

Durojaiye 2020 <https://pmc.ncbi.nlm.nih.gov/articles/PMC7298880/>

ASC Focus 2020

<https://www.ascfocus.org/ascfocus/content/articles-content/articles/2020/digital-debut/fda-updates-extended-use-drugs-list-to-meet-covid-19-demands>

Hu 2021 <https://pmc.ncbi.nlm.nih.gov/articles/PMC7919521/>

Yacouba 2021 <https://pmc.ncbi.nlm.nih.gov/articles/PMC8139224/>

Sharma 2022 <https://www.jetir.org/view?paper=JETIR2201310>

Cobicistat (Tybost/GS-9350) — Gilead's CYP3A inhibitor and pharmacokinetic booster; already approved for treating HIV/AIDS.

Stage of overall development: Approved for another indication.

Aims to target: decreasing SARS-CoV-2 viral replication and viral load; also boosts the effect of other drugs.

URLs:

Qatar Clinical Trial 2020 <https://clinicaltrials.gov/study/NCT04425382>

Shytaj et al., 2022 <https://pmc.ncbi.nlm.nih.gov/articles/PMC8941859/>

Elmekaty et al., 2022 <https://pmc.ncbi.nlm.nih.gov/articles/PMC9067693/>

Colchicine — Drug approved for other uses including in treating gout and rheumatic diseases, pericarditis and stroke; inhibits NLRP3 and reduces leukocyte inflammation.

Stage of overall development: Approved for another indication.

Aims to target: reduce the SARS-CoV-2-induced cytokine storm/inflammation.

URLs:

Yale Phase 3 Clinical Trial 2020 <https://clinicaltrials.gov/study/NCT04472611>

Montreal Phase 3 Clinical Trial 2020

<https://clinicaltrials.gov/study/NCT04322682>

Mitev 2024 <https://www.mdpi.com/2075-4426/14/7/756>

Elshiwiy et al 2024 <https://pmc.ncbi.nlm.nih.gov/articles/PMC11031948/>

Cycloferon (CMA, 10-carboxymethyl-9-acridanone) — Russian low molecular weight drug that induces interferon production, providing antiviral and immunomodulatory effects. Currently used in treatment of herpes and respiratory viral infections. Also has demonstrated direct (non-IFN-mediated) antiviral activity against adenovirus in vitro.

Stage of overall development: Preclinical.

Aims to target: SARS-CoV-2 viral persistence; immunomodulation.

URLs:

Mazin 2022 <https://www.antibiotics-chemotherapy.ru/jour/article/view/929>

Mazina 2017

<https://www.researchgate.net/publication/321955489> Clinical efficacy of the immunomodulatory agent cycloferon tablets in viral respiratory infections Results of a systematic review and meta-analysis

Zarubaev 2003

<https://www.sciencedirect.com/science/article/abs/pii/S0166354202001936>

diABZI-4 (Diamidobenzimidazole/CAS# 2138299-34-8) — InvivoGen's STING (stimulator of interferon genes) interferon agonist (synthetic compound).

Stage of overall development: Preclinical.

Aims to target: reduce inflammation; inhibit coronavirus infection by disrupting the formation of viral replication organelles.

URLs:

Invivogen1 <https://www.invivogen.com/diabzi-sting-agonist>

Song 2024 <https://onlinelibrary.wiley.com/doi/10.1002/jmv.70020>

Eukarion 8 (EUK8)— A mitochondria-targeted antioxidant that inhibits mROS (mitochondrial reactive oxygen species), thereby reducing HIF-1alpha, viral proteins, and inflammatory cytokines. Process would not be susceptible to SARS2 mutation resistance. Thus far, only tested in mice.

URLs: Jul 2024 <https://pubmed.ncbi.nlm.nih.gov/39008677/>

Galectin 1 and Galectin 3 inhibitors (Prolectin M, Galectovid, others)— Guar gum-derived carbohydrates that reduce SARS-CoV-2 viral load by competitively inhibiting viral binding to cell surface glycans.

Stage of overall development: Phase 2.

Aims to target: Reduction of SARS-CoV-2 viral load and inflammation.

URLs:

Miller 2024 <https://esmed.org/MRA/mra/article/view/5616>

Ahmed 2023

<https://pmc.ncbi.nlm.nih.gov/articles/PMC10179732/#sec2-ijms-24-08116>

Sigamani 2023 <https://pmc.ncbi.nlm.nih.gov/articles/PMC10140888/>

Sigamani 2022a

<https://assets-eu.researchsquare.com/files/rs-1531940/v1/a5d50c07-9097-4f89-8d5f-cece8a907b56.pdf?c=1659741254>

Sigamani 2022b

<https://www.researchgate.net/publication/362361449> Carbohydrate prolectin-M a galectin-3 antagonist blocks SARS-CoV-2 activity

Sigamani 2020 <https://www.medrxiv.org/content/10.1101/2020.12.03.20238840v2>);
Sakai 2022 <https://pubmed.ncbi.nlm.nih.gov/35916813/>

Interferon lambda (pegylated interferon lambda)— Reducing viral load and hyperinflammation.

Aims to target: Reduction of viral load and hyperinflammation.`

URLs: NEJM <https://www.nejm.org/doi/full/10.1056/NEJMc2303519>

McCarthy 2023 <https://pubmed.ncbi.nlm.nih.gov/37147857/>

Stanford clinical trial <https://clinicaltrials.gov/study/NCT04331899>

NACE2i— Peptide inhibitor of ACE2 that inhibits viral replication, prevents inflammation and macrophage infiltration.

Aims to target: inhibiting viral replication, preventing inflammation and macrophage infiltration.

URLs: Tu 2023 <https://www.nature.com/articles/s41467-023-39341-4>

Medical Xpress 2023

<https://medicalxpress.com/news/2023-06-drug-covid-re-infection.html>

Nitazoxanide (Alinia)— Antiprotozoal drug - antiparasitic and antiviral.

Aims to target: reduce SARS-CoV-2 viral load.

URLs: (2021 US Phase 3 Clinical Trial. <https://clinicaltrials.gov/study/NCT04359680>

Stewart 2023 <https://pmc.ncbi.nlm.nih.gov/articles/PMC10654558/>

Rocco 2021 <https://publications.ersnet.org/content/erj/58/1/2003725>

2024 South Africa Clinical Trial <https://clinicaltrials.gov/study/NCT04746183>

Brazil Clinical Trial 2020 <https://clinicaltrials.gov/study/NCT04561219>

Egypt Clinical Trial 2020 <https://clinicaltrials.gov/study/NCT04498936>

Pantethin— B5 vitamin derivative hypolipidemic agent, dimer of pantetheine, an amide analogue of pantothenic acid.

Aims to target: lower lipid and inhibit cholesterol synthesis, interfering with SARS-CoV-2 interaction with cellular cholesterol.

URLs: Abou-Hamdan 2023 <https://pmc.ncbi.nlm.nih.gov/articles/PMC9906591/>

Grewal 2024 <https://www.life-science-alliance.org/content/7/5/e202302453>

Sulfoglycodendron antivirals — Sulfoglycodendron broad-spectrum antivirals block multiprotein human heparan sulfate proteoglycans (HSPG) receptors in SARS-CoV-2.

Aims to target: neutralizing SARS-CoV-2.

URLs: Coppola 2024 <https://pubs.acs.org/doi/10.1021/acs.jcim.4c00541>

Tri-TMV (Ty1, MR17-K99Y & VHH V) — Engineered nanobody consisting of Ty1, MR17-K99Y and VHH V with neutralization activity against SARS-CoV-2.

Aims to target: neutralizing SARS-CoV-2.

Clinical data for an acute COVID-19 indication: N/A.

URLs: Hannula 2024 <https://pmc.ncbi.nlm.nih.gov/articles/PMC10986514/>

TVGN 489— Tevogen Bio’s allogeneic Cytotoxic CD8+ T lymphocytes (CTLs) immunotherapy.

Aims to target: reduce viral load; detect and kill SARS-CoV-2 infected cells.

URLs: Synapse 2024

<https://synapse.patsnap.com/article/tevogen-bio-confirms-efficacy-of-tvgn-489-against-flirt-strains-of-sars-cov-2>

Tevogen 2024

https://tevogen.com/press_release/tevogen-bio-confirms-ongoing-efficacy-of-tvgn-489-its-investigational-allogeneic-off-the-shelf-immunotherapy-against-dominant-flirt-strains-of-sars-cov-2/

Yahoo 2024

<https://finance.yahoo.com/news/tevogen-bio-announces-publication-positive-120500268.html>

BioPharm 2021

<https://www.biopharminternational.com/view/fda-clears-tevogen-bios-ind-application-for-ctl-covid-19-treatment>

Clinical Trials Arena 2022

<https://www.clinicaltrialsarena.com/news/tevogen-cell-therapy-covid/>

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[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(21\)02796-3/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02796-3/fulltext)

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PDF Copy:



Book Website:



How-To Guide

This book is designed to serve as a practical resource for researchers, industry, healthcare providers, government, and individuals living with Long Covid. It compiles evidence-based principles for treatment options, models for clinical trials, research recommendations and unmet criteria, each supported by accessible research links to facilitate informed decision-making in clinical settings. For healthcare professionals, this offers a structured overview of emerging therapeutic approaches, helping to navigate the evolving landscape of Long Covid care. For the government, this book can be used as a reference to develop new laws and education addressing the disease. For patients, it serves as a tool equipping them with the knowledge needed to discuss potential treatment options with their medical providers as well as educate and lobby for their needs. By bridging the gap between research and real-world application, we hope this book empowers both doctors and patients in their pursuit of effective management strategies.

The medical information in this publication is provided as an information resource only, and is not to be used or relied on for any diagnostic or treatment purposes. This information should not be used as a substitute for professional diagnosis and treatment.

This work has been modeled from "[A National AIDS Treatment Agenda](#)" (c. 1989)

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Version 1

